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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/613,887	07/11/2000	Kirk Hogan	HOGAN-04448	9983

23535 7590 09/11/2007

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1634	
MAIL DATE	**DELIVERY MODE**
09/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/613,887	HOGAN, KIRK	
	Examiner	Art Unit	
	Jeanine A. Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *106-125 and 127-191* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *106-125 and 127-191* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 14, 2007 has been entered.

2. This action is in response to the papers filed June 14, 2007. Currently, claims 106-125, 127-191 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

3. Any objections and rejections not reiterated below are hereby withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 106-124, 127-133, 135-150, 161-186, 189, 191 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) in view of Quane et al (Human Molecular Genetics, Vol 3, No. 3, page 471-476, 1994) or Acta Anaesthesiologica Scandinavica (Vol 39, page 139-141, 1995) and La Du (Cellular and Molecular Neurobiology, Vol 11, No. 1, page 79-89, 1991) or Pharmacogenetics (Chapter 4, pages 309-326, IDS #201) and Evans et al (Science,

Vol. 286, pages 487-491, October 1999) or Poort et al (Blood, Vol 88, No. 10, page 3698-3703, 1996) and further in view of Hoon et al. (US Pat. 6,057,105, May 2, 2000) and Hacia (Nature Genetics Supplement. Vol. 21, pages 42-47, January 1999).

Miller teaches screening a patient preoperatively to determine a risk for complications during a surgical procedure. Miller teaches that patients meet with the surgeon to prepare for surgery. Miller teaches that the surgeon often informs the patient of the anesthetic preoperative requirements and presents the patient with a letter. A sample letter is provided which illustrates the date of the surgery with the time, and instructions that "it is also important that your blood tests, urinalysis, and any other tests ordered by your doctor be completed two days before you are scheduled for surgery so that they can be reviewed by your anesthesiologist prior to surgery". Miller therefore teaches the importance of a blood test prior to surgery to identify any abnormalities.

Miller does not specifically teach analyzing the blood taken from the patient within two days prior to surgery for "two or more known genetic variations associated with two or more conditions".

However, Quane et al (herein referred to as Quane) teaches the detection of novel common mutations in ryanodine receptor gene (RYR1) in malignant hyperthermia (MH). Malignant hyperthermia (MH) is triggered in susceptible people by all commonly used inhalation anesthetics. Quane has identified Gly341Arg mutation which accounts for approximately 10% of Caucasian MHS cases (abstract). Quane specifically teaches that once an individual is diagnosed as being susceptible to MH, the anesthetics which

trigger this syndrome can be avoided (page 471, col. 2). Quane also teaches that Arg615Cys is a substitution found in 3-5% of human MH families investigated (page 472, col. 1); Arg163Cys is a substitution found in 2-3% of MHS cases. Furthermore, three other rare mutations have been reported in the RYR1 gene which are in three isolated MHS and/or CCD cases. Quane teaches that patients which have not been indicated as MH normal should always be considered MHS clinically to avoid any possibility of the individual reacting to a triggering agent during anesthesia. Misdiagnosis of MHS individual as MHN can be lethal if such a patient is exposed to triggering agents (page 474, col. 1). Quane teaches that the mutation reported satisfies the genetic criteria necessary for demonstration of a causal mutation and as such this mutation should be of significant value for MHS diagnosis by genetic means (page 474, col. 1). Quane analyzes genomic DNA from peripheral blood for the presence of the mutations (page 474, col 2).

Acta Anaesthesiologica Scandinavin (referred to as AAS) teaches that certain variants have a dramatic degree of resistance to the drug, succinylcholine (SC), because they destroy it so rapidly. AAS teaches that individuals show no regular metabolic disorder unless SC or mivacurium is given such that the condition is provoked. BchE mutations are dibucaine resistant, fluoride resistant or silent. SC and mivacurium are potentially toxic in people with BchE deficiency. AAS teaches that the principles of molecular biology tests and their application to BchE variants are well illustrates and anesthesiologists need to keep up to date about these applications. AAS also teaches that other hereditary conditions of special interest to anesthesiologists,

such as malignant hyperthermia, may be diagnosed by similar methods in a few years (page 141).

La Du et al (herein referred to as La Du) teaches butyrylcholinesterase variants which have been found in individuals who have responded abnormally to the muscle relaxant succinylcholine. Variants with increased activity are resistant to succinylcholine and may require two or three doses to achieve the desired state of paralysis (page 80).

Pharmacogenetics teaches polymorphisms of desbrisoquine hydroxylase (Cytochrome P4502D6). The structures of CYP2D gene clusters are provided. The poor metabolizers are depicted. Pharmacogenetics teaches that for drugs such as codeine and encainide it is the PM subjects who may experience therapeutic failure (page 317, col. 1). Codeine is ineffective analgesic in the 5-10% of the population who have a PM phenotype. The discovery and identification of each of these conditions has saved some lives and may prevent future fatalities or morbidities.

Evans et al (herein referred to as Evans) teaches the drug-metabolizing enzyme debrisoquine hydroxylase (CYP2D6) is polymorphic. Evans teaches that "inherited differences in drug-metabolizing capacity are generally monogenic traits and their influence on the pharmacokinetices and pharmacologic effects of medications is determined by their importance for the activation or inactiviation of drug substrates (page 487, col. 2). Evens also teaches "the effects can be profound toxicity for medications that have a narrow therapeutic index and are inactivated by a polymoprhic enzyme (for example, mercaptopurine, azathioprine, thioguanine, and fluorouracil) or reduced efficacy of medications that require activation by an enzyme exhibiting genetic

polymorphism (such as codine)" (page 487, col. 3). Evans illustrates in Figure 2, drug-metabolizing enzymes known to exhibit genetic polymorphisms with incontrovertible clinical consequences. Further, severe and potentially fatal hematopoietic toxicity that occurs when thiopurine methyltransferase-deficient patients are treated with standard doses of azathioprine or mercaptopurine. Evans teaches that "many opioid analgesics are activated by CYP2D6 rendering the 2-10% of the population who are homozygous for nonfunctional CYP2D6 mutant alleles relatively resistant to opioid analgesic effects. Thus is it not surprising that there is remarkable interindividual variability in the adequacy of pain relief when uniform doses of codeine are widely prescribed" (page 489, col. 1). Evans teaches that individualizing drug dosages can improve clinical outcome (page 491, col. 1).

Poort et al (herein referred to as Poort) teaches an 20210 AG gentoype of the prothrombin gene which is a candidate for venous thrombosis in patients. It is well known in the art that venous thromboembolism can occur without apparent cause, after surgical procedures or trauma. Poort also teaches that factor V Leiden is the most common hereditary risk factor for thrombosis. Poort teaches two genetic markers which are associated with thrombosis.

Moreover, Hoon et al. (herein referred to as Hoon) teaches the benefits of using multiple markers in detection assays. Hoon teaches using multiple markers provides increased sensitivity (abstract). Hoon teaches that marker combinations may be developed, which are particularly sensitive to the effect of therapeutic regimens on disease progress such that patients may be monitored (col. 4, lines 65-68). In a

particular example, Hoon demonstrates that number of markers was studied and that using four markers was significantly better than a single marker alone (col. 21).

Additionally, Hacia teaches mutational analysis using oligonucleotide microarrays. Hacia teaches that arrays of 1,480 oligonucleotide probes were designed to detect 37 known mutations, probes were spotted on surfaces to detect mutations in HBB, and BRCA1. Hacia teaches that arrays of 135,000 probes were used to interrogate the entire 16.6kb human mitochondrial genome from ten samples (page 44, col. 1). Chips have also been used for the simultaneous genotyping of 500 markers (page 45, col. 1). Hacia teaches that chips allow for unprecedented throughput in mutational analysis with a high degree of accuracy (page 46, col. 2). Hacia teaches mutations are detected by a minisequencing assay using an algorithm. The data obtained is placed in a computer which is encrypted, but accessible to readers, i.e. decoded.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have sampled patients prior to subjecting the patient to anesthetics, as taught by Miller, to determine whether they were at risk of MH, a dramatic degree of resistance to the drug, succinylcholine (SC), resistant to succinylcholine, desbrisoquine hydroxylase, or venous thromboembolism, as taught by Quane, Acta Anaesthesiologica Scandinavica, La Du , Pharmacogenetics, Evans or Poort . Miller teaches that it is routine to sample patients blood to analyze the blood for abnormalities including hematocrit levels. Miller teaches that "the laboratory evaluation should be available for review by the anesthesiologist prior to or at the time he first sees

the patients preoperatively so that any questions regarding the patient's status should be resolved then and if not resolved the surgery should be delayed" (page 1325). Quane provides three examples of common mutations within the RYR1 gene which are associated with MH and which trigger MH syndrome during anesthesia, and potentially death. Quane specifically states that "once an individual is diagnosed as being susceptible to MH, the anesthetics which trigger this syndrome can be avoided" (page 471, col. 2). AAS teaches that SC and mivacurium are potentially toxic in people with BchE deficiency. La Du et al teaches butyrylcholinesterase variants which have been found in individuals who have responded abnormally to the muscle relaxant succinylcholine and the variants with increased activity are resistant to succinylcholine and may require two or three doses to achieve the desired state of paralysis (page 80). Pharmacogenetics teaches that codeine is ineffective analgesic in the 5-10% of the population who have a PM phenotype. Evens also teaches "the effects can be profound toxicity for medications that have a narrow therapeutic index and are inactivated by a polymoprhic enzyme (for example, mercaptopurine, azathioprine, thioguanine, and fluorouracil) or reduced efficacy of medications that require activation by an enzyme exhibiting genetic polymorphism (such as codine)" (page 487, col. 3). Additionally, Port teaches that factor V Leiden is the most common hereditary risk factor for thrombosis and two genetic markers which are associated with thrombosis.

Thus, the ordinary artisan would have been motivated to test patients within two days prior to surgery for mutations within the RYR1, CYP2D6, Prothrombin, BCHE genes for the expected benefit of determining whether the patient possessed any

mutations which were linked to the known condition of MH to avoid any fatal reaction to the anesthesia, for example. The ordinary artisan would have recognized that blood samples are routinely taken within two days prior to surgery and therefore to minimize inconvenience to the patient, the blood sample taken would also be an ideal sample for testing the patient for genetic abnormalities within RYR1. The ordinary artisan would have clearly recognized the benefit of testing an individual prior to surgery and subjection to the anesthesia for known genetic markers associated with a condition which was triggered by anesthetics.

The ordinary artisan would have then taken the results from the genetic tests and selected a perioperative course of action that was consistent with the results obtained from the genetic marker information. Moreover, once the selection was completed, the medical professionals would have performed the surgical procedure according to these directions to ensure the safety of the patient.

Moreover, given the teachings of Hoon and Hacia that sampling multiple markers provides increase sensitivity, the ordinary artisan would also be motivated to have sampled additional markers which are associated with complications in surgery. Therefore, the skilled artisan would have additionally analyzed a patient for a dramatic degree of resistance to the drug, succinylcholine (SC), resistant to succinylcholine, desbrisoquine hydroxylase, or venous thromboembolism, as taught by Acta Anaesthesiologica Scandinavica, La Du, Pharmacogenetics, Evans or Poort. Given the state of the art with relation to known markers and detecting the markers as indicative of certain disease which either trigger episodes when exposed to anesthetics, or are poor

metabolizers or potentially cause thrombosis are well known. The ordinary artisan would have been motivated to have screened individuals within two days prior to surgery to determine the genetic composition of the individuals to provide individualized diagnosis. Thus, the ordinary artisan would have been motivated to test patients within two days prior to surgery for mutations within any of the known genes for known mutations which are associated with known conditions for the expected benefit of determining whether the patient possessed any mutations which were linked to the known conditions such that the clinician may avoid any adverse reactions to the surgical procedure. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the vast number of teachings, as exemplified by the extremely voluminous Information Disclosure Statement filed, to screen individuals prior to surgery for several genetic markers which are indicative of any number of conditions which are caused by anesthesia or are a result of anesthesia. Hacia teaches that large numbers of probes are placed on arrays for the express benefit of high-throughput mutational analysis with a high degree of accuracy (page 46, col. 2). The ordinary artisan would have recognized that the art provides a large number of single nucleotide polymorphisms or other variations which are indicative of conditions. The benefit of screening individuals for several of these prevalent mutations which are related to surgery would have allowed the anesthesiologist to determine whether plausible substitutes may be provided to patients which would not cause these conditions to arise. Specifically, detection of RYR1 polymorphisms which are associated with MH would indicate to the anesthesiologist that drugs which trigger the

episodes should be avoided. Moreover, codeine should be administered with care to individuals having certain BchE mutations. Combining more than one screening method to determine the genomic profile of a patient would have provided the anesthesiologist with a more complete picture of the patients genetic make-up. As suggested in many of the articles, individual treatment and screening is ideal for analysis of the genetic make-up of patients.

With respect to the claims drawn to invasive and non-invasive surgery, anesthesia and codine, for example are administered routinely in each of these situations.

With respect to the claims drawn to specific numbers of markers, for example 5 and 10 or more mutations, the skilled artisan would be motivated to screen makers which were well known at the time of the art simultaneously or in tandem for the benefits of providing the most complete amount of information possible. Hacia specifically teaches that arrays to detect mutations of approximately 500 were known in the art at the time the invention was made.

With respect to Claim 149, the newly added limitations are all directed to obtaining consent, and distributing the results according to patient's preference. Miller specifically obtains consent based upon the consent form and signature on page 1325 of Miller. Furthermore, the results of the analysis that the patient is receiving would be distributed to those individuals who could make an informed decision to the course of action. These individuals would be according the patience preference.

With respect to Claim 187-188, Hacia teaches mutations are detected by a minisequencing assay using an algorithm. The data obtained is placed in a computer which is encrypted, but accessible to readers, i.e. decoded.

Response to Argument

The Response traverses the rejection. The response filed September 27, 2006, January 2004, July 23, 2004 and the brief filed September 21, 2005 asserts that the cited art fails to establish prima facie obviousness. The claims are drawn to testing two or more nucleic acid markers in two or more genes associated with two or more conditions and selecting a course of action based on the information from the profile. The Response asserts that the Board and the Examiner have failed to establish a prima facie case of obviousness. As specifically provided by 706.07(h), "In addition to the res judicata effect of a Board of Patent Appeals and Interferences decision in an application (see MPEP § 706.03(w)), a Board decision in an application is the "law of the case," and is thus controlling in that application and any subsequent, related application." The applicant had the opportunity to appeal any Board decision from which they were dissatisfied. The response raises many issues and concerns with regard to the Board and the Examiner's position. It is noted that as provided in 35 U.S.C. 141. "An applicant dissatisfied with the decision in an appeal to the Board of Patent Appeals and Interferences under section 134 of this title may appeal the decision to the United States Court of Appeals for the Federal Circuit. By filing such an appeal the applicant waives his or her right to proceed under section 145 of this title."

The response, page 18, assert that none of the Examiner's references disclose all elements of the claimed invention and the Examiner has failed to provide a suggestion or motivation to combine the elements to yield the claimed invention. The extensive arguments will be responded in the order presented in the response.

II.A.1.a- The response asserts that the combination fails to teach selecting a perioperative course of action based upon information from the perioperative genomic profile and performing a surgical procedure.

The response asserts Claim 106 requires selecting a perioperative course of action based upon information from the genomic profile. The examiner fully agrees with this assertion. However, given the cited combination of references, once the ordinary artisan realized that a patient was predisposed to have an adverse reaction to anesthesia or other condition, the ordinary artisan would have selected a course of action consistent with this discovery and acted appropriate. Doctors are subject to liability. In the event that the skilled doctor did not heed the warnings of a genetic test performed, liability would attach. Thus, the ordinary artisan would have been motivated to have taken what was determined and discovered from the genetic profile and used the information in a prudent manner to avoid any complications that may exist given the information generated from the genetic analysis.

Moreover, as previously argued and affirmed by the Board, It would have been obvious once the genomic profile was selected, that a perioperative course of action based on the information from the profile would be followed. It is clear that previous

Claim 86 from appeal already positively recited this additional method step and was affirmed by the Board.

The response asserts that the references fail to provide any guidance to the anesthesiologist, nurse or surgeon to use the information (see page 20 of the response filed). This argument has been reviewed but is not persuasive. The information obtained from a genomic profile would be information that the surgeon, anesthesiologist and nurses would use. Specifically, Quane teaches variants in the RYR1 gene which are associated with poor response to anesthesia. This information would be information appropriate for anesthesiologists to have in order to prescribe and administer the appropriate anesthesia to a patient.

II.A.1.b. The response argues that the combination of references is missing the limitation that a perioperative course of action is for the first surgerical procedure for the subject (claim 107). This argument has been reviewed but is not persuassive. The ordinary artisan would be motivated to screen patients for any and all surgeries to ensure precautions are taken to prevent any complications.

II.A.1.c The response argues that the combination of references is missing the limitation that the course of action comprisise administration of anesthesia during a medical procedure. This argument has been reviewed but is not persuassive. The Quane references teaches that "once an individual is diagnosed as being susceptible to MH, the anaestheics which trigger this syndome can be avoided." This passage

illustrates that not ALL anesthesia is avoided, but those that trigger this syndrome are avoided. Thus, the course of action would contain anesthesia, but be modified to include an anesthetic which does not trigger MH.

II.A.1.d The response argues that the combination of references is missing the limitation that the genomic profile comprises information comprising presymptomatic risk. This argument has been reviewed but is not persuassive. The ordinary artisan would be motivated to screen patients for any and all surgeries to ensure precautions are taken to prevent any complications before signs are shown. The ordinary artisan would be motivated to test for MH prior to triggering a response that would cause death.

II.A.1.e. The response argues that the combination of references is missing the limitation that the genomic profile comprises information pertaining to differential diagnosis of co-existing diseases (limitations of Claim 121). This argument has been reviewed but is not persuassive. The ordinary artisan would be motivated to diagnose the specific condition that is associated with poor resonse to anesthesia. The analysis of the MH gene would allow for differential diagnosis between MH and other anesthesia triggering conditions. Once the differential diagnosis is performed the appropriate response by the medical professional can be performed.

II.A.1.f. The response asserts Claim 127 requires selecting a surgical procedure treatment course of action based upon information from the genomic profile. The

examiner fully agrees with this assertion. However, given the cited combination of references, once the ordinary artisan realized that a patient was predisposed to have an adverse reaction to anesthesia or other condition, the ordinary artisan would have selected a course of action consistent with this discovery and acted appropriate. Doctors are subject to liability. In the event that the skilled doctor did not heed the warnings of a genetic test performed, liability would attach. Thus, the ordinary artisan would have been motivated to have taken what was determined and discovered from the genetic profile and used the information in a prudent manner to avoid any complications that may exist given the information generated from the genetic analysis.

II.A.1.g. The response asserts that the combination of elements fails to teach a profile that consists of alleles in the BchE, CYP2D6, MTHFR, MTR, CBS, F2, F5, RYR1, CACNA1S, CPT2 and TNFalpha. This argument has been reviewed and the claim is rejected below in view of the specification.

II.A.1.h The response asserts that the combination of elements fails to teach a non-invasive surgical procedure. This argument has been reviewed but deemed not persuasive. The ordinary artisan would be motivated to screen patients for any and all surgeries to ensure precautions are taken to prevent any complications before signs are shown. The ordinary artisan would be motivated to test for MH prior to triggering a response that would cause death.

II.A.1.i. The response asserts that the combination of elements fails to teach selection of monitoring procedures based upon the profile. This argument has been reviewed but deemed not persuasive. The ordinary artisan would have been motivated to have monitored procedures. Poort specifically teaches an 20210 AG gentoype of the prothrombin gene which is a candidate for venous thrombosis in patients. It is well known in the art that venous thromboembolism can occur without apparent cause, after surgical procedures or trauma. Poort also teaches that factor V Leiden is the most common hereditary risk factor for thrombosis. Poort teaches two genetic markers which are associated with thrombosis. Thus, in the event that the patient's profile indicated the presence of markers known to be associated with venous thrombosis, the nurses and doctors would have monitored the patient more closely for signs of venous thrombosis.

II.A.1.j. The response asserts that the combination of references is missing the element of obtaining consent from a perioperative subject to assay a sample for genetic variation (Claim 149). Despite Miller teaching obtaining consent for perioperative tests and analysis, the response asserts this is not consent for a genetic variation test. This argument has been reviewed but is not persuasive. The ordinary artisan would have been motivated to have obtained consent for ANY procedure in the medical field, as is routine and customary in the field, to avoid any malpractice allegations. It is routine in the art that any procedure requires authorization and consent. Individuals who are

subjected to surgery sign consent forms routinely. Thus, requiring consent from a subject prior to the perioperative genomic profiling would have been obvious.

II.A.1.k. The response asserts that the combination of references is missing the element of distributing the results of a patients profile to include destroying the results or saving the results. This argument has been reviewed but is not persuasive. The ordinary artisan would have either destroyed the results or saved the results. It is not apparent what other choices were available to the patient. Thus, the ordinary artisan would have been motivated to have done one of these two actions.

II.A.1.l. The response asserts that the combination of references is missing the element of distributing the sample to include destroying the sample or saving the sample. This argument has been reviewed but is not persuasive. The ordinary artisan would have either destroying the sample or saving the sample. It is not apparent what other choices were available to the patient. Thus, the ordinary artisan would have been motivated to have done one of these two actions.

II.A.1.m. The response asserts that the combination of references is missing the element of a computer program comprising instructions which direct a processor to analyze results of a perioperative genomic profile. This argument has been reviewed but is not persuasive. Hacia teaches mutations are detected by a minisequencing

assay using an algorithm. The data obtained is placed in a computer which is encrypted, but accessible to readers, i.e. decoded.

II.A.1.n-II.A.1.w. The response asserts that combination fails to teach certain elements. In view of the newly presented rejection below over Lapointe, these arguments are moot.

II.A.1.x. The response asserts that the combination of references is missing the element of teaching pre-operative phenotypic tests and consultation. This argument has been reviewed but is not persuasive. The response asserts that the references fail to teach performing pre-operative pheyotypic tests and consultation, however, it was routine at the time the invention to provide for analysis of phenotypic tests including weight, height, as taught by Miller.

II.A.1.y. The response asserts that combination fails to teach certain elements. In view of the newly presented rejection below over Lyamichev, these arguments are moot.

II.A.1.z The response asserts that the combination of references is missing the element of teaching of a kit comprising a computer program. This argument has been reviewed but is not persuasive. The use of computer programs to analyze data, was specifically illustrated by Hacia. Hacia teaches mutations are detected by a minisequencing assay using an algorithm. The data obtained is placed in a computer which is encrypted, but

accessible to readers, i.e. decoded. The providing of the computer and algorithm meets the requirements of a kit. A kit, without more, is merely a composition of reagents.

II.A.1.aa. The response asserts that the combination of references is missing the element of teaching of a kit for generating a perioperative genomic profile. This argument has been reviewed but is not persuasive. The use of computer programs to analyze data, and generate results, i.e. genomic profile, was specifically illustrated by Hacia. Hacia teaches mutations are detected by a minisequencing assay using an algorithm. The data obtained is placed in a computer which is encrypted, but accessible to readers, i.e. decoded. The providing of the computer and algorithm meets the requirements of a kit. A kit, without more, is merely a composition of reagents.

II.A.1.bb.-IIA.1.cc. In view of the newly presented rejection below over Lapointe, these arguments are moot.

II.A.1.dd The response asserts that the combination of references fails to teach selecting the markers by analytical validity, clinical validity and clinical utility. This argument has been reviewed but is not persuasive. The ordinary artisan would have selected those markers, as discussed above, based upon these three criteria. Analyzing markers which have no utility or validity would not have been motivated by the art.

II.A.1.ee. The response asserts that combination fails to teach certain elements. In view of the newly presented rejection below over Lapointe, these arguments are moot.

II.A.2. The response asserts that there is no motivated to combine the cited references. The response states that "the examiner has failed to indicate where in the references there is such a suggestion of desirability to combine. The response continues that the requirement that the examiner make a showing of a suggestion, teaching or motivation to combine the prior art references is an essential evidentiary component of an obviousness holding. This argument has been considered but is not convincing because the holding of KSR specifically rejects the rigid TSM test and finds that the references need not provide a specific motivation in the references. The cited passage from KSR illustrates an analysis must be made specific, not that the TSM is explicit. The analysis of KSR allows for a person with ordinary skill to have good reason to pursue known options within his or her technical grasp. Moreover, KSR discusses the use of ordinary skill and common sense. Thus, the rigid test of TSM is no longer required to be explicitly found within the references.

The declaration filed by Dr. Douglas Coursin under 1.132 has been considered. The declaration under 37 CFR 1.132 filed on June 14, 2007 is insufficient to overcome the rejection as set forth in the last Office action because: it states that the claimed subject matter solved a problem that was long standing in the art. However, there is no showing that others of ordinary skill in the art were working on the problem and if so, for

how long. In addition, there is no evidence that if persons skilled in the art who were presumably working on the problem knew of the teachings of the above cited references, they would still be unable to solve the problem. See MPEP § 716.04. Here, the declaration of Dr. Coursin fails to provide any evidence in the opinion declaration that the ordinary skilled artisans were working on the problem and for how long. Moreover, the declaration fails to provide any evidence that those working in the art on the problem knew of the Quane, Miller, Acta Anaesthesiologica Scandinavica, La Du, Pharmacogenetics, Evans et al, Poort et al , Hoon et al. or Hacia references and were still unable to solve the problem. Thus, the declaration is insufficient to overcome the 103 rejection of record.

The response, page 40, appears to suggest that Dr. Coursin provided unexpected results for the claimed subject matter. As provided in MPEP 716.02(a) evidence must show unexpected results. The opinion declaration submitted by Dr. Coursin does not appear to show any unexpected results. The declaration provided by Dr. Coursin, states that many genetic markers were found to exist in patients and that there was significant genetic heterogeneity not accounted for in family history check-boxes. The discovery that individuals contain heterogeneity is not unexpected. The art of record clearly illustrates the frequency of various alleles within the population. It is not unexpected that screening for genetic mutations known to be associated with deleterious outcomes and death, are present in humans. In fact it is completely expected given all of the teachings of the art. Moreover, it is completely not unexpected

that detecting these genetic mutations can avoid deleterious outcomes and save lives. This is the basis of the entire 103 rejection.

Thus, for the reasons above and those already of record, the rejection is maintained.

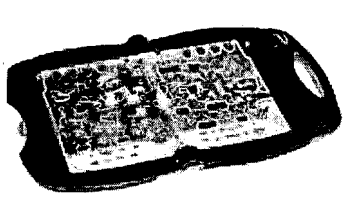
5. Claims 151-160, 187-188, 190 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) in view of Quane et al (Human Molecular Genetics, Vol 3, No. 3, page 471-476, 1994) or Acta Anaesthesiologica Scandinavica (Vol 39, page 139-141, 1995) and La Du (Cellular and Molecular Neurobiology, Vol 11, No. 1, page 79-89, 1991) or Pharmacogenetics (Chapter 4, pages 309-326, IDS #201) and Evans et al (Science, Vol. 286, pages 487-491, October 1999) or Poort et al (Blood, Vol 88, No. 10, page 3698-3703, 1996) and further in view of Hoon et al. (US Pat. 6,057,105, May 2, 2000) and Hacia (Nature Genetics Supplement. Vol. 21, pages 42-47, January 1999) as applied to Claims 106-124, 127-133, 135-150, 161-186, 189, 191 above and further in view of Lapointe et al. (US 6,678,669, January 2004).

Miller, Quane, AAS, LaDu, Pharmoacogenetics, Poort, Hoon and Hacia do not specifically teach processing and selecting medical tests using computer programs to predict information.

However, Lapointe teaches obtaining patient data or information, typically patient history or clinical data, and analyzing by the decision-support systems to identify important or relevant variables and decision-support systems are trained on the patient

data. Lapointe specifically illustrates in Figure 2, the interaction of the biochemical and the computer network to generate predictive information. As seen in Figure 13 and 16, the input of data spots out test report forms that are understandable and translate into treatment options. The decision-support systems are employed to evaluate specific observation values and test results, to guide the development of biochemical or other diagnostic tests, too assess a course of treatment, to identify new diagnostic tests and disease markers, to identify useful therapies, and to provide the decision-support functionality for the test. Lapointe teaches that the final set of networks is trained to perform the diagnosis. Lapointe teaches that the biochemical tests can include any test from which useful diagnostic information may be obtained.

Therefore, it would have been prima facie obvious at the time the invention was made to have designed a neural network as taught by Lapointe for the perioperative screening method of Miller, Quane, AAS, LaDu, Pharmoacogenetics, Poort, Hoon and Hacia. Lapointe specifically teaches that biochemical data is inputed from patient data and analyzed to produce guides to medical personnel to assess course of treatments. The ordinary artisan would have been motivated to have automated the analysis to enable non-biochemically inclined individuals to understand the output of genomic studies in an understandable and useable manner. Lapointe specifically illustrates throughout the document the outputs provided from the software contains the meanings of the results in plain language. All the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions and the combination would have



yielded predictable results to one of ordinary skill in the art at the time the invention. Specifically, the ordinary artisan in the biochemical fields would have found it obvious to update the biochemical assays which required analysis and reading by a human with modern networks and decision trees on a computer, as taught by Lapointe, in order to gain the commonly understood benefits of such adaptation such as increased reliability, understandable readout, and simplified operation. See Leepfrog v. Fisher-Price (Fed. Cir. 2007).

6. Claim 185 is rejected under 35 U.S.C. 103(a) as being unpatentable over Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) in view of Quane et al (Human Molecular Genetics, Vol 3, No. 3, page 471-476, 1994) or Acta Anaesthesiologica Scandinavica (Vol 39, page 139-141, 1995) and La Du (Cellular and Molecular Neurobiology, Vol 11, No. 1, page 79-89, 1991) or Pharmacogenetics (Chapter 4, pages 309-326, IDS #201) and Evans et al (Science, Vol. 286, pages 487-491, October 1999) or Poort et al (Blood, Vol 88, No. 10, page 3698-3703, 1996) and further in view of Hoon et al. (US Pat. 6,057,105, May 2, 2000) and Hacia (Nature Genetics Supplement. Vol. 21, pages 42-47, January 1999) as applied to Claims 106-124, 127-133, 135-150, 161-186, 189, 191above and further in view of Lyamichev et al. (Nature Biotechnology, Vol. 17, pages 2925-296, March 1999).

Miller, Quane, AAS, LaDu, Pharmoacogenetics, Poort, Hoon and Hacia do not specifically teach analyzing DNA using structure-specific cleavage of oligonucleotide probes assay.

However, Lyamichev teaches polymorphism detection and identification using quantitative detection of genomic DNA by invasive cleavage of oligonucleotide probes. Lyamichev specifically teaches that the invader assays are sensitive and specific to allow discrimination of single-base differences and can differentiate homozygotes from heterozygotes in single-copy genes in genomic DNA. Lyamichev teaches that a major advantage of the invader assay is the requirement for coordinated action of the invasive and signal probes. The probes together confer a high degree of specificity and simplicity.

Therefore, it would have been prima facie obvious at the time the invention was made to have modified the detection methods of Miller, Quane, AAS, LaDu, Pharmoacogenetics, Poort, Hoon and Hacia to encompass invader directed analysis as taught by Lyamichev. Lyamichev specifically teaches the invader assays are simple, specific and highly sensitive to avoid false positive results.

7. Claims 125 and 134 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) in view of Quane et al (Human Molecular Genetics, Vol 3, No. 3, page 471-476, 1994) or Acta Anaesthesiologica Scandinavica (Vol 39, page 139-141, 1995) and La Du (Cellular and Molecular Neurobiology, Vol 11, No. 1, page 79-89, 1991) or Pharmacogenetics (Chapter 4, pages 309-326, IDS #201) and Evans et al (Science, Vol. 286, pages 487-491, October 1999) or Poort et al (Blood, Vol 88, No. 10, page 3698-3703, 1996) and further in view of Hoon et al. (US Pat. 6,057,105, May 2, 2000) and Hacia (Nature Genetics Supplement. Vol.

21, pages 42-47, January 1999) as applied to 106-124, 127-133, 135-150, 161-186, 189, 191 above and further in view of the specification (Tables 1-4).

Miller, Quane, AAS, LaDu, Pharmoacogenetics, Poort, Hoon and Hacia do not specifically teach profiling for each of BchE, CYP2D6, MTHFR, MTR, CBS, F2, F5, RYR1, CACNA1S, CTP2, and TNFA.

The instant specification teaches markers in each of these genes which are associated with various operative related disorders. The specification clearly illustrates genes and mutations which are associated with the particular mutations (see page 48-49 and the cited references). The response filed March 26, 2001 specifically illustrates that the invention does not claim discovery of newly identified DNA sequences (page 7).

Therefore, it would have been obvious in view of the teachings of Miller, Quane, AAS, LaDu, Pharmoacogenetics, Poort, Hoon and Hacia to include any number of genes on the array of Hacia for the highthroughput analysis of operatives complications that were known at the time of the invention. The prosecution history of this application indicates that the invention does not claim discovery of newly identified sequences, thus, it would have been obvious to include the analysis of any of the known mutations in the art.

Response to Arguments

The response traverses the rejection. The response asserts it is unclear what is meant by the specification clearly illustrates genes and mutations which are associated with particular mutations. This argument has been reviewed. The specification, pages 48-49 clearly illustrates the genes of the claims and the cited references. Moreover, the

prosecution history clearly states that the invention does not claim discovery of newly identified DNA sequences (page 7). Thus, the ordinary artisan would have profiled the genes recited in the claims to enable the analysis of the particular conditions associated with the alleles.

II.C.2. The response asserts that there is no motivated to combine the cited references. The response states that "the examiner has failed to indicate where in the references there is such a suggestion of desirability to combine. The response continues that the requirement that the examiner make a showing of a suggestion, teaching or motivation to combine the prior art references is an essential evidentiary component of an obviousness holding. This argument has been considered but is not convincing because the holding of KSR specifically rejects the rigid TSM test and finds that the references need not provide a specific motivation in the references. The cited passage from KSR illustrates an analysis must be made specific, not that the TSM is explicit. The analysis of KSR allows for a person with ordinary skill to have good reason to pursue known options within his or her technical grasp. Moreover, KSR discusses the use of ordinary skill and common sense. Thus, the rigid test of TSM is no longer required to be explicitly found within the references. Thus for the reasons above and those already of record, the rejection is maintained.

New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 125, 134, 160, 186 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the amended claims, reference to "TNFalpha" are included. The amendment suggests support is found on page 2, 25 and 29. Instead the specification describes discusses genes in Tables 1-4. It is noted that the CIP application has added the TNF gene, but this parent application does not refer to TNFalpha. This description does not support TNFalpha. The concept of markers within "TNFalpha" does not appear to be part of the originally filed invention. Therefore, "TNFalpha" constitutes new matter. Applicant is required to cancel the new matter in the reply to this Office Action.

Response to Arguments

The response traverses the rejection. The response asserts the specification provides ample and explicit support for TNF alpha at page 2, page 25 and page 29. This argument has been considered but is not convincing because the support pointed to does not appear to correspond with any analysis of the TNF alpha gene. On page 2, lines 26-28 discusses sepsis as a major cause of death, but fails to disucc any genes. On page 25, the page only contains 29 lines. Thus, line 33 does not support the amendment. Finally, page 29, lines 9-15 are directed to B1 adrenergic receptors and cytochormoe p450, but makes no mention of TNF alpha. Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

Jeanine Goldberg
Primary Examiner
September 4, 2007